Lifetime Health Advisories (HA) for Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA)

U.S Environmental Protection Agency
Office of Water

Process for Development of Lifetime HAs

- **2014 Draft Health Effects Support Documents**
  - Developed by OW, with support from ORD/NCCT on pharmacokinetic modeling.
  - Internally reviewed by OSWER, OCSPP, OCHP, and ORD in 2014.
  - Presented to state health officials through presentations at Federal-State Toxicology Risk Analysis Committee (FSTRAC).
- **2014 Public Panel Peer Review**
  - Followed EPA's 2013 *Conflict of Interest Review Process for Contractor-Managed Peer Reviews of EPA HISA and ISI Documents*.
    - Three Federal Register Notices: 1) released draft documents for 60-day public comment period and solicited panel nominations, 2) published interim list of panel members for public comment, and 3) announced final panel and meeting details.
  - Panel included 7 experts in the following areas: epidemiology, toxicology (liver, immune, neurological and reproductive and developmental effects), membrane transport, risk assessment, pharmacokinetic models, and mode-of-action for cancer and noncancer effects.
  - Public comments on the draft documents were provided to the panel prior to the panel meeting in August 2014.

Process for Development of Lifetime HAs (Cont'd)

- **Final Health Effects Support Documents and Lifetime Health Advisories**
  - OW considered the comments from the expert panel and the public and revised the documents accordingly, with support from ORD/NCCT on pharmacokinetic modeling.
  - Final draft documents were internally reviewed by ORD, OLEM, OCHP, OCSPP. ORD/NCEA provided assistance on summaries of epidemiological data.
  - Final draft documents were circulated for review by other federal partners, including ATSDR, CDC, FDA, NIEHS (NIOSH), CPSC, OSHA, and NTP.

Health Advisories (HA) Calculations

- HAs are non-regulatory information for federal, state and local officials to consider when addressing drinking water contamination.

- Lifetime HAs are calculated using the following equation:

$$\boldsymbol{Lifetime\ HA} = \left(\frac{RfD * BW}{DI}\right) * RSC$$

  - Where:
    - **RfD** is the Reference Dose-An RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure of the human population to a substance that is likely to be without an appreciable risk of deleterious effects during a lifetime.
    - **BW** is bodyweight – the mean bodyweight of the target population.
    - **DI** is drinking water intake – the 90th percentile drinking water intake rate for the target population.
    - **RSC** is the Relative Source Contribution – the percentage of an individual's exposure to the compound that is expected to come from drinking water exposure.

Summary of Health Effects

- PFOA and PFOS health effects information is available from animal studies and human epidemiology studies.
- Animal studies were used quantitatively to develop candidate RfDs. Human epidemiology studies were used as additional supporting lines of evidence.
- Studies indicate that PFOA and PFOS exposure results in multiple health effects including: developmental effects, effects on serum lipids and total cholesterol, liver and kidney effects, immune effects, reproductive effects, and cancer.
- Under EPA's Cancer Guidelines there is *Suggestive* evidence of carcinogenic potential for both PFOA and PFOS.
  - PFOA-Positive association for kidney and testicular cancers from epidemiology literature and liver, testicular, and pancreatic tumors in rats.
  - PFOS-No positive associations from epidemiology literature and evidence of liver adenomas and thyroid in rats (lacked dose-response).

Animal Pharmacokinetic Approach

- EPA used a peer-reviewed pharmacokinetic model (Wambaugh et al. 2013) to calculate average serum concentrations associated with candidate NOAELs and LOAELs.
- The Wambaugh et al. (2013) model is based on the Andersen et al. (2006) concept that clearance of PFOA/PFOS is rapid at high concentrations and slow at low concentrations, resulting in the long serum half-lives seen in humans and animals.
- A unique feature of the pharmacokinetic approach is the use of a single model for the three species and reliance on the serum levels as the measure of exposure.
- PK data was available for each species, and species-specific pharmacokinetic parameters were estimated using Bayesian analysis (which includes sensitivity analysis)
- A nonhierarchical model for parameter values was assumed wherein a single numeric value represented all individuals of the same species, gender, and strain. Body weight, the number of doses, and magnitude of the doses were the only parameters that varied.
- The use of the model indicated consistency in the average serum values associated with effect and no-effect doses across species
  - **This finding reduced the uncertainty associated with interspecies variability**

Human Pharmacokinetic Approach

- Average serum levels that the model showed to be consistent across species were then used to determine human equivalent doses.
- No human PK time course data available to calibrate Andersen et al. (2006) model, so a simpler "one compartment" model was used
- Humans were assumed to be at steady state
- For half-life ($t_{½}$):
  - PFOA: Bartell et al. (2010) determined a human half-life of 2.3 years based on the decline in serum levels among members of the general population exposed via drinking water
  - PFOS: Olsen et al. (2007) calculated the half-life in this former worker population as 5.4 years
- For volume of distribution (V_d) Thompson et al. (2010) gives a V_d of 0.17 L/kgbw for PFOA and 0.23 L/kg BW for PFOS
- The $t_{½}$ and V_d are utilized to calculate the CL

$$CL = V_d \times \left(\frac{\ln 2}{t_{1/2}}\right)$$

- For PFOA CL = 1.4 x 10^{-4} L/kg bw/day, for PFOS CL = 8.1 x 10^{-5} L/kg bw/day
- Human Equivalent Dose (HED) = average serum concentration (in mg/L) x CL

Reference Dose (RfD) Selection

- EPA extensively reviewed the available literature addressing multiple toxicological endpoints and modeled average serum values using a peer-reviewed pharmacokinetic model (rat, mouse, and monkey) to derive RfDs for these two chemicals.
- EPA modeled data from multiple studies for effects on development; liver; and the immune system where available.
- For both chemicals, the RfDs developed from multiple studies of both short-term and longer-term exposures and based on various adverse effects fall within a narrow range.
- For each chemical, EPA selected the RfD based on developmental effects to calculate a health advisory protective for the general population and sensitive lifestages.

Candidate RfD Values – PFOA

Selected Quantification Results from Critical Studies

Reference	Endpoint	PK-HED (mg/kg/day)	UF_H	UF_A	UF_L	UF_S	UF_D	Total	RfD (mg/kg/day)
Palazzolo et al. 1993	rat liver effects	0.0044 (NOAEL)	10	3	1	1	1	30	0.00015
Dewitt et al. 2008	mouse immune effects	0.0054 (NOAEL)	10	3	1	10	1	300	0.00002
Lau et al. 2006	**mouse delayed ossification and early male puberty**	**0.0056 (LOAEL)**	**10**	**3**	**10**	**1**	**1**	**300**	**0.00002**
Butenhoff et al., 2004	rat adult body and kidney weight	0.0064 (LOAEL)	10	3	10	1	1	300	0.00002
Wolfe et al 2007 (17 days)	mouse pup body weight	0.0115 (LOAEL)	10	3	10	1	1	300	0.00004
Wolfe et al 2007 (11 days)	mouse pup body weight	0.0134 (LOAEL)	10	3	10	1	1	300	0.00004

Candidate RfD Values – PFOS

Selected Quantification Results from Critical Studies									
Reference	**Endpoint**	**PK-HED (mg/kg/day)**	**UF_H**	**UF_A**	**UF_L**	**UF_S**	**UF_D**	**Total**	**RfD (mg/kg/day)**
Seacat et al. 2002	monkey liver effects	0.0031 (NOAEL)	10	3	1	1	1	30	0.0001
Seacat et al. 2003	rat liver effects	0.0013 (NOAEL)	10	3	1	1	1	30	0.00004
Lau et al. 2003	rat pup survival	0.0014 (NOAEL)	10	3	1	1	1	30	0.00005
Butenhoff et al. 2009	rat neuro effects	0.00084 (NOAEL)	10	3	1	1	1	30	0.00003
Luebker et al. 2005b	**rat pup weight**	**0.00051 (NOAEL)**	**10**	**3**	**1**	**1**	**1**	**30**	**0.00002**
Luebker et al. 2005a	rat pup weight	0.0016 (LOAEL)	10	3	3	1	1	100	0.00002

Critical Studies and Effects Selected as Basis for RfDs

PFOA

- Lau et al., 2006
  - Developmental toxicity study
  - Dosing throughout pregnancy gestational days 1-17; pups sacrificed at weaning (e.g., lactational exposure included)
- Decreased ossification in proximal phalanges and accelerated puberty in male pups
- Total UF = 300 (10 for intraspecies differences, 3 for interspecies differences, 10 for LOAEL to NOAEL extrapolation)
- **RfD = 2 x 10-5 ug/kg-day**

PFOS

- Luebker et al., 2005b
  - 2-generation reproductive toxicity study
  - Dosing premating and throughout pregnancy and lactation for 2 generations
- Decreased body weight and weight gain in pups
- Total UF = 30 (10 for intraspecies differences, 3 for interspecies differences)
- **RfD = 2 x 10-5 ug/kg-day**

Relative Source Contribution (RSC)

- The RSC is the percentage of an individual's exposure to the compound that is expected to come from drinking water exposure.
- EPA derived an **RSC of 20% for PFOA and PFOS** for the national HA, meaning exposure is primarily through other sources (e.g., dust, air, soil, etc.); reserve 20% of RfD to account for exposure via drinking water.
- The RSC of 20% is based on available occurrence information and considering the environmental persistence of these compounds:
  - CDC data provide evidence of broad exposure to PFAS from multiple sources.
  - Currently, diet is the major source of PFOA and PFOS:
  - Indoor dust is another major source (especially to children) from treated carpets and furniture/textiles in homes, offices, automobiles.
  - Other sources of legacy exposure or exposure to precursors: soils, air, clothing, cosmetics, cleaning materials, etc.

Exposure Scenario

- Due to the potential increased susceptibility during the time period of pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women in the calculation of a Lifetime HA for this target population during this potential critical time period.
- EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90th percentile for lactating women (see Table 3-81 in U.S EPA, 2011).
- Comparing between the pregnant and lactating woman, the lactating woman is the most sensitive given her increased water intake rate (54 mg/L-day) to support milk production.
- Additionally, human studies have shown that PFOA and PFOS are transferred from mother to infant via cord blood and breast milk. A recent study showed that breast milk contributed > 94% and > 83% of the total PFOS and PFOA exposure, respectively, in 6-month-old infants (Haug et al., 2011).

Lifetime HA Calculation for PFOA and PFOS

$$\text{Lifetime HA} = \frac{\text{RfD} \times \text{RSC}}{\text{DWI/BW}}$$

Where:

HA = Health Advisory

RfD = Reference Dose [0.00002 mg/kg/d]

RSC = Relative Source Contribution [20%]

DWI/ BW = DWI adjusted by BW for lactating women [0.054 L/kg]

$$\text{Lifetime HA} = \frac{0.00002 \text{ mg/kg/d} \times 0.2}{0.054 \text{ L/kg}}$$

Lifetime HA = 0.00007 mg/L

= 0.07 µg/L

Lifetime HA and Application

- **The Lifetime HAs are based on developmental effects resulting from exposures that occur during pregnancy and lactation (nursing) and are protective for all other health effects (non-cancer and cancer) that may occur during a lifetime of exposure to these chemicals in drinking water.**
  - For developmental effects, a single exposure at a critical time in development may produce an adverse outcome, i.e., repeated exposure is not a necessary prerequisite for toxicity to be manifested (US EPA 1991). These effects (i.e., low birth weight) can impact an individual over a lifetime.

- PFOA and PFOS are extremely persistent in both the human body and the environment; thus, even a short-term exposure results in a body burden that persists for years and can increase if additional exposure occurs later.

Lifetime HA and Application

- Because the critical effects identified are developmental effects and can potentially result from a short-term exposure during a critical period of development, the Lifetime HAs apply to both short term, such as the time periods during pregnancy and nursing and bottle feeding, as well as chronic (lifetime) exposure scenarios.

- Because the toxicological effects and the potency of PFOA and PFOS are very similar, where these chemicals co-occur in drinking water at the same time, we recommend that the HA be applied to the sum of the concentrations of PFOA and PFOS.
  - EPA has not evaluated the toxicity of other PFAS at this time.

EPA Recommendations for Drinking Water Systems

- If water sampling results confirm that drinking water contains PFOA and PFOS at individual or combined concentrations greater than 70 parts per trillion, water systems should:
  - Promptly notify State drinking water agency and consult on the best approach to conduct additional sampling.
  - Promptly provide consumers with information about the levels of PFOA and PFOS in their drinking water.
    - This notice should include specific information on the risks to fetuses during pregnancy and breastfed and formula-fed infants.
    - Include actions that consumers may consider to reduce risk such as seeking an alternative drinking water source, or in the case of parents of formula-fed infants, using formula that does not require adding water.

EPA Recommendations for Drinking Water Systems

- A number of options are available to drinking water systems to lower concentrations of PFOA and PFOS in their drinking water supply:
  - closing contaminated wells or changing rates of blending of water sources;
  - treat source water with activated carbon or high pressure membrane systems (e.g., reverse osmosis);
  - providing bottled water to consumers while steps to reduce or remove PFOA or PFOS from drinking water;
  - some home drinking water treatment units are certified by independent accredited third party organizations against American National Standards Institute (ANSI) standards to verify PFOA and PFOS removal claims.

ATSDR Draft Toxicological Profile

- ATSDR derived minimal risk levels (MRLs) for 4 PFAS (PFOA, PFOS, PFHxS, PFNA). ATSDR is the first federal agency to derive toxicity values for PFAS other than PFOA and PFOS.
  - MRLs are ATSDR's "equivalent" to EPA's reference doses (RfDs).
- ATSDR's MRLs for PFOA and PFOS are about 10 times lower (more conservative) than EPA's RfDs.
  - ATSDR used the same pharmacokinetic model used by EPA.
  - Study selection:
    - For PFOA, ATSDR selected critical studies and effects different than EPA. EPA considered one of these studies but did not select it as the critical study. The second study was published after the HAs were released. Both of these studies are single dose rather than a series of doses.
    - For PFOS, ATSDR selected the same critical study and effect as EPA but applied an additional uncertainty factor to account for immunotoxicity. EPA evaluated available immunotoxicity studies and included a detailed characterization of these effects, but did not apply an additional uncertainty factor due to inconsistencies across the studies.
- OW provided comments on ATSDR's draft Toxicological Profile (coordinated through EPA's OSA) in June 2017.